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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/940,692	09/30/1997	FERNANDO VALLE	GCL266-2	5194

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GENENCOR INTERNATIONAL, INC.
ATTENTION: LEGAL DEPARTMENT
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EXAMINER

PROUTY, REBECCA E

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/940,692	Applicant(s) Valle et al.
	Examiner Rebecca Prouty	Art Unit 1652
<i>-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --</i>		
Period for Reply		
A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.		
<ul style="list-style-type: none"> - Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication. - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely. - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). - Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b). 		
Status		
1) <input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>Dec 23, 2002</u>		
2a) <input checked="" type="checkbox"/> This action is FINAL. 2b) <input type="checkbox"/> This action is non-final.		
3) <input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11; 453 O.G. 213.		
Disposition of Claims		
4) <input checked="" type="checkbox"/> Claim(s) <u>23-27, 29-31, 33-40, and 42-51</u> is/are pending in the application.		
4a) Of the above, claim(s) _____ is/are withdrawn from consideration.		
5) <input checked="" type="checkbox"/> Claim(s) <u>39, 40, 43, 47, 48, and 51</u> is/are allowed.		
6) <input checked="" type="checkbox"/> Claim(s) <u>23-27, 29-31, 33-38, 42, 44-46, 49, and 50</u> is/are rejected.		
7) <input type="checkbox"/> Claim(s) _____ is/are objected to.		
8) <input type="checkbox"/> Claims _____ are subject to restriction and/or election requirement.		
Application Papers		
9) <input type="checkbox"/> The specification is objected to by the Examiner.		
10) <input type="checkbox"/> The drawing(s) filed on _____ is/are a) <input type="checkbox"/> accepted or b) <input type="checkbox"/> objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).		
11) <input type="checkbox"/> The proposed drawing correction filed on _____ is: a) <input type="checkbox"/> approved b) <input type="checkbox"/> disapproved by the Examiner. If approved, corrected drawings are required in reply to this Office action.		
12) <input type="checkbox"/> The oath or declaration is objected to by the Examiner.		
Priority under 35 U.S.C. §§ 119 and 120		
13) <input type="checkbox"/> Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).		
a) <input type="checkbox"/> All b) <input type="checkbox"/> Some* c) <input type="checkbox"/> None of: 1. <input type="checkbox"/> Certified copies of the priority documents have been received. 2. <input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____. 3. <input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).		
*See the attached detailed Office action for a list of the certified copies not received.		
14) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e). a) <input type="checkbox"/> The translation of the foreign language provisional application has been received.		
15) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.		
Attachment(s)		
1) <input type="checkbox"/> Notice of References Cited (PTO-892)		
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)		
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____		
4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____		
5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)		
6) <input type="checkbox"/> Other: _____		

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A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-23-02 has been entered.

Claims 1-22, 28, 32 and 41 have been canceled. Claims 23-27, 29-31, 33-40, 42-46 and newly presented Claims 47-51 are still at issue and are present for examination.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 23, 27, 38, 41, 45, 46, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined disclosures of Saier et al and Ingrahm et al.

Saier et al. teach methods of selecting a $\text{Pts}^-/\text{glucose}^+$ cell comprising deleting the PTS genes (*ptsH* and *ptsI*), culturing the mutant cell using glucose as the sole available carbon source and selecting cells with a fast growth rate on glucose. The fastest growth rate specifically obtained by the mutants of Saier et al. was 0.35/hr. Applicants claimed methods recite selecting cells with a growth rate of at least 0.4/hr.

Ingrahm et al. teach that it would be advantageous to increase the supply of PEP in a cell used for production of a desired product, in particular aromatic amino acid production, by modifying an enteric bacteria such as *E. coli* to use an alternative pathway from the PTS system for glucose uptake such that PEP production is not obligately coupled to glucose transport.

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Therefore, as Ingrahm et al. disclose that Pts⁻/glucose⁺ cells are particularly useful for production of desired products one of ordinary skill in the art would have been motivated to screen for Pts⁻/glucose⁺ cells such as those of Saier et al. with even higher growth rates than those specifically disclosed by Saier et al. As Saier et al. disclose cells with growth rates very close to the claimed rate of at least 0.4/hr one of ordinary skill in the art would have reasonably expected to be able to obtain cells within the scope of the claims.

First it should be noted that the previous rejection was made over the combined disclosures of Saier et al and Ingrahm et al. This was immediately apparent from both the text of the rejection which used motivation from Ingrahm to suggest modifying Saier et al. as well as from the statement of the rejection which stated that it was obvious over the disclosures of Saier et al **and** Ingrahm et al. and not obvious over the disclosure of **either** Saier et al **or** Ingrahm et al. which would have been used if the references were taken individually.

Applicants dispute the examiner's contention that there would be a reasonable expectation of success to isolate Pts⁻/glucose⁺ cells with growth rates at least 0.4/hr in view of the showing of such cells by Saier et al. with growth rates of

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0.35/hr. Applicants state that the 0.05/hr difference in growth rates correspond to a difference in generation time of 14.6% and an increase in glucose consumption of 12.6%. Applicants further point to Neidhardt as teaching that a change in growth rate from 0.6 to 1.0 produces significant changes in cell parameters such as the number of ribosomes per cell and the rate of mRNA synthesis per cell. Applicants arguments have been considered but are not persuasive to overcome the rejection. Saier et al. teach **two** mutant strains (SB2637 and SB2634) which meet all limitations of the instant claims except for the recited growth rate limitation (and not four as stated by applicants as only 2 of the four strains shown in Table 1 of Saier et al. have been selected for growth on glucose as the sole carbon source). It should be noted that Saier et al. report generation times using only one significant digit in the numbers reported such that a growth rate of 0.4/hr (which is equivalent to a generation time of 1.7 hrs) would have been reported as 2 hrs when rounded off to a single significant digit, while a generation time of 0.8/hr (which corresponds to a generation time of 52 min) would have been reported as 1 hr when rounded off to a single significant digit. As such it is not even certain that the growth rate of the two mutant strains reported by Saier et al. do not in fact

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meet the limitations of the instant claims. However, even if the growth rate of these mutant strains isolated by Saier et al. is slightly lower than the 0.4/hr limitation recited in the claims, it is certainly sufficiently close that one of ordinary skill in the art would have expected to be able to isolate similar Pts⁻/glucose⁺ cells with growth rates as claimed. The reference of Neidhardt actually supports the examiners position as Neidhardt is reporting significant differences between strains with growth rate differences which are substantially larger, i.e. a difference of 0.4/hr (analogous to the difference between 0.4/hr and 0.8/hr) than the difference in growth rate between the cells of Saier et al. and the cells of the current claims, i.e., 0.05/hr. There is no evidence in Saier et al. of major differences in cells with growth rate differences as small as 0.05/hr. Applicants discussion of the differences in how the mutant cells with increased growth rates on glucose were obtained between Saier et al. (which treated the Pts⁻ cells with nitrosoguanidine and then grew the treated cells on minimal glucose agar) and applicants (which cultured Pts⁻ cells under continuous culture conditions with glucose as the sole carbon source in order that only glucose⁺ spontaneous mutants would grow) is noted but not persuasive to overcome the rejection as both methods would have been recognized in the art as equivalent

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alternatives for isolating mutants of Pts⁻ cells that would grow on glucose as the sole carbon source. The method by which the mutation is generated (whether chemically induced or spontaneous) is irrelevant to a showing that such mutations can be isolated. Therefore, as Ingrahm et al. clearly provide motivation for the skilled artisan to desire Pts⁻/glucose⁺ cells with increased growth rates, and the disclosure of Saier et al. provides a reasonable expectation that such cells could be obtained, the instant claims as *prima facie* obvious. It should be noted that *prima facie* obviousness does not require a showing of absolute certainty of success but only a reasonable expectation thereof.

Claims 23-27, 29-31, 33-38, 42, 44, 45, 46, 49, and 50 are rejected under 35 U.S.C. § 103 as being unpatentable over the combined disclosures of Frost, Holms, Ingrahm et al. and Saier et al.

Frost teaches the amplification of carbon flow into the common aromatic pathway by increasing the amount of one of the substrates (E4P) for the first committed step of this pathway (i.e., the DAHP synthetase catalyzed condensation of E4P and PEP) by introduction of the transketolase gene into the host cell. He further teaches the introduction of one or more of the genes of

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the common aromatic pathway in such cells to further increase the amount of the desired final product.

Holms teaches that PEP within *E. coli* is consumed by several different metabolic pathways (i.e., the PTS system, pyruvate synthesis by pyruvate kinase, and oxaloacetate synthesis by phosphoenolpyruvate carboxylase) and the amount of PEP channeled into each of these pathways. Holms teaches that the PTS system consumes 66% of the PEP produced while only 3% of the PEP pool is channeled into aromatic amino acid synthesis.

Ingrahm et al. teach that it would be advantageous to increase the supply of PEP in a cell used for production of a desired product, in particular aromatic amino acid production, by modifying an enteric bacteria such as *E. coli* to use an alternative pathway from the PTS system for glucose uptake such that PEP production is not obligately coupled to glucose transport.

Saier et al. teach methods of selecting a *Pts⁻/glucose⁺* cell which uses galactose permease to transport glucose comprising deleting the PTS genes (*ptsH* and *ptsI*), culturing the mutant cell using glucose as the sole available carbon source and selecting cells with a fast growth rate on glucose.

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The disclosure of Frost of amplification of carbon flow into the common aromatic pathway by increasing the amount of one of the substrates (E4P) for the first committed step of this pathway would suggest to the ordinary skilled artisan the amplification of the other necessary precursor (i.e., PEP) of this enzymatic step as this would assure that neither substrate for this enzyme would be in limiting supply. One of ordinary skill in the art would recognize that the supply of any precursor used by a cellular pathway could be amplified by either increasing the amount of the precursor synthesized (such as done by Frost for E4P) or by preventing the depletion of the precursor by other cellular pathways thereby increasing the amount of the precursor available to be used by the desired pathway. The disclosure of Holms that 66% of the cellular PEP is used by the competing PTS pathway would suggest to the ordinary skilled artisan that PEP availability to the common aromatic pathway could be substantially increased by preventing PEP use by the PTS pathway. Furthermore, Ingrahm et al. explicitly suggest this as an approach to increasing the level of carbon flow into the common aromatic pathway. The disclosure of Saier et al. shows that it is possible to produce cells which are deleted in the PTS system yet still retain high growth rates on glucose (a carbon source normally transported by the deleted PTS system) by utilizing the

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galactose permease as a means of glucose transport. Therefore, it would have been obvious to one of ordinary skill in the art to produce a $\text{Pts}^-/\text{glucose}^+$ mutant of the host cells of Frost which exhibit high levels of carbon flow into the common aromatic pathway as one of ordinary skill in the art would reasonably expect such a mutant cell to divert higher levels of the cellular pool of PEP into the aromatic amino acid biosynthetic pathways and produce further increases in the amount of carbon flow into this pathway. It would have been further obvious to one of ordinary skill in the art to select for such cells with high growth rates as such cells would be expected to be most useful for producing large amounts of aromatic amino acids.

Furthermore, it would have been further obvious to one of ordinary skill in the art to further increase the amount of PEP diverted into this pathway by preventing its use by the other metabolic pathways which Holms teach that it is consumed by. As such it would have been obvious to further mutate the pyruvate kinase and pyruvate carboxylase genes as well.

The discussion of the rejection above is incorporated herein with regard to the instant rejection to support the examiner's position with regard to the expectation of obtaining $\text{Pts}^-/\text{glucose}^+$ cells with the claimed 0.4/hr growth rate.

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In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants do not appear to respond the rejection which states that the **combined** disclosures of Frost, Holms, Ingrahm et al. and Saier et al. make obvious the instant rejection instead merely pointing out which elements of the claims are lacking in each reference. It is acknowledged that each reference individually does not teach or suggest the claimed invention, however, the **combined** disclosures clearly provide the skilled artisan all of a suggestion, a motivation, and a reasonable expectation of success of obtaining the claimed invention. As such the claimed invention is *prima facie* obvious.

Claims 39, 40, 43, 47, 48, and 51 are allowable.

These claims are limited to cells having a specific growth rate of at least 0.8/hr or methods of using such cells. Saier et al. fail to teach that one can obtain PTS⁻/glu⁺ cells with a growth rate this high. While one of ordinary skill in the art would clearly have been motivated to look for cells with higher growth rates than those obtained by Saier et al. (as discussed

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above), the ordinary skilled artisan would expect that limitations on the ability of the cell to transport glucose might inhibit the rate of growth of the cells on this sugar such that one could not reasonably expect that cells with such a substantially higher growth rate could be obtained without a demonstration thereof. As such it would have merely been obvious to try to obtain cells with this claimed higher growth rate.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened

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statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Rebecca Prouty
Primary Examiner
Art Unit 1652